UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/493,427	01/29/00	IVERSON	P 0450-0025.30

022918
IOTA PI LAW GROUP
350 CAMBRIDGE AVENUE SUITE 250
P O BOX 60850
PALO ALTO CA 94306-0850

HM22/1204

EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	4

DATE MAILED: 12/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/493,427	Applicant(s) IVERSON ET AL.	
	Examiner Janet L Epps	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 January 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

In the first line of the specification, Applicants have stated that the instant application is a continuation-in-part (CIP) of US provisional application 60/117,846. This claim to priority is improper since a CIP application may only be filed from a non-provisional application. The first line of the specification should state that the instant application claims the benefit of US provisional application 60/117,846 filed January 29, 1999.

Sequence Information

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The applicant did not submit a CRF with this application.

A complete response to this Office Action requires that Applicants comply with the sequence rules, and that pending rejections be addressed. Any response that does not address all of these issues will be held as non-responsive. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 13-14, and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the tunica media". There is insufficient antecedent basis for this limitation in the claim. Claim 1 also recites the limitation "the compound," this claim only provides support for the limitation "the antisense compound."

Claims 2-4, 13-14, and 17-18, recite references to a particular figure in the specification. The figures that Applicants are referring to do not provide appropriate definitions of the various substituents of the structures in the figures, namely Z, X, and Y_2. In addition, where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

Reference characters corresponding to elements recited in the detailed description and the drawings may be used in conjunction with the recitation of the same element or group of elements in the claims. See MPEP § 608.01(m).

Claim 6 recites the phrase "drive the compound into region of the vessel," this phrase is vague and indefinite since the meaning of the term "region of the vessel" is unclear.

Claim 8 recites the limitation "channels that communicate with a distal-tip," the meaning of the term "communicate" as used in this context is vague and indefinite.

Claim 10 recites the limitation "is entrapped form," the metes and bounds of the meaning of this phrase is vague and indefinite.

Claims 11 and 12 recite the limitation "the coating" in claim 1, claim 1 only provides support for the limitation "the hydrogel coating."

Claims 1-15 and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim restating the preamble.

Claims 17-22 recite the limitation "the compound," in claim 16, claim 16 only provides support for the limitation "the antisense compound."

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1, 6-10, 16, and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Zalewski et al.

Claim 1, and those claims dependent therefrom, read on a method for reducing the risk of restenosis in a region of a risk of restenosis in a patient's coronary vessel which has been treated by coronary angioplasty using a catheter with a distal-end expandable balloon, or which is at a junction formed in a coronary bypass operation, comprises locally administering directly to the vessel site of injury, a morpholino antisense compound (I) having 8-40 nucleotides, including a targeting base sequence that is complementary to a region that spans the start codon of a human c-myc mRNA gene, and uncharged, phosphorus-containing intersubunit linkages. The mode of administration is selected from the following: (a) contacting the region of the vessel with a reservoir containing (I) and introducing it from the reservoir into the vessel by iontophoresis or electroporation; (b) injecting the compound from the catheter directly into the region of the vessel, under pressure, through injectors contained on the surface of the catheter balloon, where the injectors are capable of penetrating the tunica media in the vessel; (c) injecting into or contacting the region of the vessel, microparticles containing (I) in entrapped form; (d) contacting the region of the vessel with a hydrogel coating contained on the surface of the catheter balloon, and containing (I) in diffusible form; or (e) contacting the region of the vessel with a stent having an outer surface layer containing (I) in diffusible form.

Zalewski et al. teach antisense oligonucleotides targeting human *c-myc* for the treatment of excess extracellular matrix in the tissues of a patient. The antisense oligonucleotides of Zalewski et al. may comprise morpholino modifications and modified phosphorous containing intersubunit linkages such as as phosphorothioate, phosphorodithioate, phosphoramidate, or methylphosphonate. The antisense oligonucleotides of the Zalewski et al. invention have lengths in the range of about 12 to about 60 nucleotides, preferably in the range of about 15 to about 40

and most preferably they have lengths in the range of about 18 to 30 nucleotides (col. 9, lines 15-21). The antisense oligonucleotides of this invention are preferably targeted to the initiation codon site, the mRNA donor splice site, the 5' cap site, tRNA primer binding site, and the mRNA acceptor splice site (col. 7, lines 5-10).

Zalewski et al. also teach that their disclosed antisense oligonucleotides can be used for intravascular application, in order to prevent restenosis after angioplasty. The antisense oligonucleotides are preferably administered in the vicinity of the lesion via catheter from inside the lumen, or through the adventitia (i.e. the most outer layer of the vessel wall) with materials aiding a slow release of antisense compound, e.g. a pluronic gel system, a porous balloon or iontophoretic balloon (col. 10, lines 55-67). Additionally, the Zalewski et al. invention comprises the use of sustained release systems suitable for administration of the antisense oligonucleotide compositions, these systems include semi-permeable polymer matrices in the form of films, microcapsules, or the like, comprising polylactides, copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, poly(2-hydroxyethyl methacrylate), and like materials. These sustained release systems also include liposomally entrapped antisense compounds (col. 16-27).

Zalewski et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalewski et al. as discussed above in view of Kobayashi et al., Summerton et al., and Agrawal et al.

The discussion of Kalewski et al. as set forth above is included in this rejection. Kalewski et al. discloses a method for preventing restenosis in a patient comprising the administration of antisense oligonucleotides comprising a morpholino and modified phosphorous containing intersubunit linkages, to the site of injury in a patient. However, Kalewski et al. does not teach the administration of a c-myc antisense oligonucleotides comprising the nucleotides sequence as set forth in SEQ ID NO:1 of the instant application, nor does Kalewski et al. teach the phosphorodiamidate linkage represented at Figure 2B-B, where X=NH_2, Y=O, and Z=O. Kalewski et al. does not teach the administration of antisense oligonucleotides in an amount between 0.5 and 20mg, or in a solution containing at least about 30 mg/ml of the antisense compound. In addition, Kalewski et al. does not teach the use of a derivatized antisense compound comprising a triethyleneglycol moiety.

Kobayashi et al. teach the use of antisense oligonucleotides targeting the translation initiation sites of c-myc. These antisense oligonucleotides suppressed the proliferation of MKN-45, a human gastric cancer-derived cell line, and DLD-1, a human colon cancer-derived cell line, in vitro and in vivo. The antisense oligonucleotides comprise phosphorothionate type

modifications. The c-myc AO suppressed MKN-45 cell proliferation in vitro at concentration from 0.1-10 mM, and 70% of suppression was obtained with 3-10 mM concentration. The AO decreased the ratio of c-myc positive cells, and the intracellular concentration of c-myc mRNA. Intratumor injection of AO for c-myc (27 mer, AACGTTGAGGGG CATCGTCGCGGGAGG, 10 mM) suppressed the tumor growth of MKN-45 transplanted to the BALB/c mouse. The c-myc antisense oligonucleotide of Kobayashi et al. comprises the nucleotide sequence of SEQ ID NO:1 of the instant application (abstract).

Summerton et al. disclose alpha-morpholino ribonucleoside derivatives and polymers thereof, which are capable of sequence-specific binding to polynucleotides. These alpha-morpholino subunits form stable uncharged linkages and can be used to generate polymers having an uncharged backbone. According to Summerton et al., standard ribo- and deoxyribonucleotide polymers suffer from a number of limitations when used for base-specific binding to target oligonucleotides. These limitations include (i) restricted passage across biological membranes, (ii) nuclease sensitivity, (iii) target binding which is sensitive to ionic concentration, and (iv) susceptibility to cellular strand separating mechanisms. Furthermore, Summerton et al. state that these limitations can be overcome or minimized by designing polynucleic acid analogs in which the bases are linked along an uncharged backbone (col. 2, lines 10-23).

Agrawal et al. teach modifications which enhance oligonucleotide solubility. In one embodiment Agrawal et al. discloses oligonucleotides comprising a triethyleneglycol moiety.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to modify the method of preventing restenosis in a patient as described by

Kalewski et al. with the antisense oligonucleotide of Kobayashi et al. because this antisense oligonucleotide has been disclosed to function successfully in vitro and in vivo to reduce the expression of c-myc. Furthermore, one of skill in the art would have been motivated to use the antisense oligonucleotides of Kobayashi et al. because it would have been obvious to replace one functionally equivalent antisense oligonucleotide targeting c-myc with another. In addition, it would have been obvious to one of ordinary skill in the art to modify the antisense oligonucleotides of Kalewski et al. with the alpha-morpholino modified subunits of Summerton et al. since these polymers comprising these subunits are disclosed as being capable of overcoming the limitations described above that are associated with polymers comprising a charged backbone. One of ordinary skill in the art would have been motivated to use the modified polymers of Summerton et al. in the method of Zalewski et al., because using polymers having enhanced biological activity would provide a means to increase the therapeutic efficacy of potential pharmaceutical agents.

Moreover, it would have been obvious to one of ordinary skill in the art to modify the oligonucleotides of Kalewski et al. with triethyleneglycol modifications as described by Agrawal, since these modifications enhance the solubility of the antisense oligonucleotides. Furthermore, one of ordinary skill in the art would have been motivated to use antisense oligonucleotides having enhanced solubility as modified by the method of Agrawal et al. since these antisense oligonucleotides are to be used in an aqueous biological environment. Agrawal et al. also teach that these moieties can be used to form oligonucleotide multimers, such multimers would enhance the effective concentration of the oligonucleotide and therefore increase the efficacy of an antisense compound.

Applicant's method recites the use of an antisense compound in an amount of about 0.5 to 2 mg or in a solution containing at least about 30 mg/ml. Kalewski et al. teach the use of antisense oligonucleotides in their disclosed methods in amount of between about 1 to 100 μM and more preferably between 1 to 10 μM. Although the method of Kalewski et al. does not recite the exact amount of antisense compound as recited in Applicant's method it would have been obvious to one of ordinary skill in the art to optimize the conditions of an experiment or reaction in order to maximize the desired results.

Therefore, the invention as a whole is *prima facie* obvious over Kalewski et al. in view of Kobayashi et al. and Summerton et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps whose telephone number is 703-308-8883. The examiner can normally be reached on Mondays through Friday between the hours of 9AM and 6PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

jle
November 30, 2000

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600